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Fr m: Mosher, Mary
Sent: Thursday, July 10, 2003 8:27 AM
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Gene Therapy (1997) 4, 16-24. *9068791*
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DIALOG(R) File 155:MEDLINE(R)

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10886415 97238259 PMID: 9084579

Characterization of recombinant adeno-associated virus-2 as a vehicle for gene delivery and expression into vascular cells.

Gnatenko D; Arnold T E; Zolotukhin S; Nuovo G J; Muzyczka N; Bahou W F

Department of Medicine, State University of New York at Stony Brook 11794-8151, USA.

Journal of investigative medicine - the official publication of the American Federation for Clinical Research (UNITED STATES) Feb 1997, 45

(2) p87-98, ISSN 1081-5589 Journal Code: 9501229

Contract/Grant No.: HL49141; HL; NHLBI; HL50257; HL; NHLBI; HL53665; HL; NHLBI; +

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

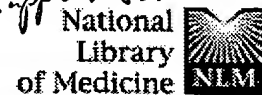
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BACKGROUND: We have used wild-type and recombinant adeno-associated virus-2 (AAV) to study transduction, replication efficiencies, functional protein expression, and gene delivery to vascular cells in vitro and in vivo. METHODS: Recombinant adeno-associated virus-2 (rAAV) plasmids (ranging in size to 110% of wild-type AAV) driven by 6 distinct promoters upstream of a beta-galactosidase cassette were effectively used for generation of replication-deficient virus, with titers consistently ranging from 2.5×10^5 IU/mL. AAV infectivity and replication in human umbilical vein endothelial cells (HUVEC) were unrelated to cellular proliferative index establishing the potential utility of the virus for transduction of quiescent vascular cells. Long-term cultures of AAV-infected HUVEC established the presence of episomal forms at 18 days, although chromosome 19-specific integration was not evident. Functional beta-galactosidase activity approximately 400% above control was evident in HUVEC using either a murine collagen alpha 1(I) promoter (pTRCol alpha 1(I) beta) or CMV promoter (pTRCMV beta). RESULTS: Based on these initial data, in vivo studies were completed using a rat carotid artery model. Both wild-type AAV (titers -1×10^9 IU/mL) and rAAV (pTRCol alpha 1(I) beta or pTRCMV beta) efficiently infected vascular cells in vivo with endothelial and vascular smooth muscle cell transduction frequencies approaching 90% as judged by DNA in situ polymerase chain reaction, with no evidence for disrupted vessel architecture. Protein expression using total vessel extracts at 48 hours postinfection demonstrated 20-fold increase in functional beta-galactosidase activity using pTRCol alpha 1(I) beta compared to saline-injected controls vessels (799 +/- 236 microU/mg protein vs 40.7 +/- 17 microU/mg protein). CONCLUSIONS: These data provide the first evidence that rAAV may be adapted for directed high-level transgene delivery and expression into normally quiescent vascular endothelial and smooth muscle cells both in vitro and in vivo.

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☐ 1: Exp Neurol. 1998 Apr;150(2):183-94.

Related Articles, Links

NEUROSCIENCE
FULL-TEXT ARTICLE

Neuron-specific transduction in the rat septohippocampal or nigrostriatal pathway by recombinant adeno-associated virus vectors.

Klein RL, Meyer EM, Peel AL, Zolotukhin S, Meyers C, Muzyczka N, King MA.

Department of Pharmacology and Therapeutics, University of Florida, Gainesville, Florida 32610, USA.

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Related Resources

Viral vector-mediated gene transfer in brain can provide a means for gene therapy and functional studies. However, robust and persistent transgene expression in specific populations of the adult brain has been difficult to achieve. In an attempt to produce localized and persistent transduction in rat brain, we compared recombinant adeno-associated virus (rAAV) vectors incorporating either the immediate early cytomegalovirus (CMV) promoter or the neuron-specific enolase (NSE) promoter. Transduction in hippocampus resulting from the NSE promoter-containing construct was more efficient and persistent than that resulting from the CMV promoter-containing construct. Most hippocampal cells transduced with the NSE promoter had multipolar neuron morphology. Neurons with glutamatergic morphology were transduced weakly. In order to produce a local supply of neurotrophic factor to cells that degenerate under certain disease and experimental conditions, the NSE promoter was utilized to drive expression of brain-derived neurotrophic factor (BDNF) in medial septum or substantia nigra. In this construct, the NSE promoter drives dicistronic expression of BDNF and an enhanced version of green fluorescent protein (GFP). We estimated 3000-15,000 GFP-positive cells per injection of rAAV into septum or substantia nigra, a transduction ratio of 5-20 infectious virus particles per transduced cell. This frequency may be sufficient for trophic factor gene therapy as well as for investigating specific protein function in "topical (i.e., localized) transgenic" animals produced by rAAV. Copyright 1998 Academic Press.

MeSH Terms:

- Animal

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06350292 89366639 PMID: 2771638

Analysis of the collagen alpha 1(I) promoter.

Brenner D A; Rippe R A; Veloz L

Center for Molecular Genetics, University of California, San Diego 92093.

Nucleic acids research (ENGLAND) Aug 11 1989, 17 (15) p6055-64,

ISSN 0305-1048 Journal Code: 0411011

Contract/Grant No.: DK07202; DK; NIDDK

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

The collagen alpha 1(I) gene is regulated at a developmental and tissue specific level. We have previously demonstrated that only 220bp of the promoter region of the collagen alpha 1(I) gene are required for efficient expression in NIH 3T3 cells. DNase I protection assays demonstrated 4 footprinted segments in the promoter region. Deletional analysis revealed that the 3 most proximal footprints were required for maximal expression. The most proximal footprint contains a CCAAT sequence and a 12bp segment that forms a direct repeat with the preceding footprint. Ligation of the proximal footprint sequence to a heterologous promoter enhanced transcription of the reporter gene. These studies, therefore, identify and characterize elements in the promoter region of the collagen alpha 1(I) gene that interact with DNA binding proteins and are required for efficient expression.

Record Date Created: 19890929

Record Date Completed: 19890929

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DIALOG(R)File 155:MEDLINE(R)

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RC 321, E94

11317641 98197132 PMID: 9527887

Neuron-specific transduction in the rat septohippocampal or nigrostriatal pathway by recombinant adeno-associated virus vectors.

Klein R L; Meyer E M; Peel A L; Zolotukhin S; Meyers C; Muzyczka N; King M A

Department of Pharmacology and Therapeutics, University of Florida, Gainesville, Florida 32610, USA.

Experimental neurology (UNITED STATES) Apr 1998, 150 (2) p183-94, ISSN 0014-4886 Journal Code: 0370712

Contract/Grant No.: AG00196; AG; NIA; GM 35723; GM; NIGMS; PPG AG10485; AG; NIA; +

Document type: Journal Article

7/7/2

DIALOG(R)File 155:MEDLINE(R)

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14731982 22302496 PMID: 12413421

Promoters and regulatory elements that improve adeno-associated virus transgene expression in the brain.

Fitzsimons Helen L; Bland Ross J; During Matthew J

CNS Gene Therapy Center, Department of Neurosurgery, Thomas Jefferson University, Philadelphia, PA 19107, USA.

Methods (San Diego, Calif.) (United States) Oct 2002, 28 (2) p227-36
, ISSN 1046-2023 Journal Code: 9426302

Document type: Journal Article; Review; Review Literature

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Since the first demonstration of central nervous system (CNS) transduction with recombinant adeno-associated virus, improvements in vector production and promoter strength have lead to dramatic increases in the number of cells transduced and the level of expression within each cell. The improvements in promoter strength have resulted from a move away from the original cytomegalovirus (CMV) promoter toward the use of hybrid CMV-based promoters and constitutive cellular promoters. This review summarizes and compares different promoters and regulatory elements that have been used with rAAV as a reference toward achieving a high level of rAAV-mediated transgene expression in the CNS. Copyright 2002 Elsevier Science (USA) (69 Refs.)

Record Date Created: 20021104

Record Date Completed: 20030423

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14731981 22302495 PMID: 12413420

Regulation of gene expression in adeno-associated virus vectors in the brain.

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Methods (San Diego, Calif.) (United States) Oct 2002, 28 (2) p219-26
, ISSN 1046-2023 Journal Code: 9426302

Document type: Journal Article; Review; Review, Tutorial

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Regulated adeno-assoc